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Metastatic Infectious Disease and Clinical Outcome in *Staphylococcus aureus* and *Streptococcus* species Bacteremia

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Abstract: Early detection of metastatic infection in patients with Gram-positive bacteremia is important as morbidity and mortality are higher in the presence of these foci, probably due to incomplete eradication of clinically silent foci during initial treatment. We performed a prospective study in 115 patients with *Staphylococcus aureus* or *Streptococcus* species bacteremia with at least 1 risk factor for the development of metastatic foci, such as community acquisition, treatment delay, persistently positive blood cultures for >48 hours, and persistent fever >72 hours after initiation of treatment. An intensive search for metastatic infectious foci was performed including ^{18}F-fluorodeoxyglucose-positron emission tomography in combination with low-dose computed tomography scanning for optimizing anatomical correlation (FDG-PET/CT) and echocardiography in the first 2 weeks of admission.

Metastatic infectious foci were detected in 84 of 115 (73%) patients. Endocarditis (22 cases), endovascular infections (19 cases), pulmonary abscesses (16 cases), and spondylodiscitis (11 cases) were diagnosed most frequently. The incidence of metastatic infection was similar in patients with *Streptococcus* species and patients with *S. aureus* bacteremia. Signs and symptoms guiding the attending physician in the diagnostic workup were present in only a minority of cases (41%). An unknown portal of entry, treatment delay >48 hours, and the presence of foreign body material were significant risk factors for developing metastatic foci. Mean C-reactive protein levels on admission were significantly higher in patients with metastatic infectious foci (74 vs. 160 mg/L).

FDG-PET/CT was the first technique to localize metastatic infectious foci in 35 of 115 (30%) patients. As only a minority of foci were accompanied by guiding signs or symptoms, the number of foci revealed by symptom-guided CT, ultrasound, and magnetic resonance imaging remained low.

Mortality tended to be lower in patients without complicated infection compared to those with metastatic foci (16% vs. 25%, respectively). Five of 31 patients (16%) without proven metastatic foci died. In retrospect, 3 of these 5 patients likely had metastatic foci that could not be diagnosed while alive. In patients with Gram-positive bacteremia and a high risk of developing complicated infection, a structured protocol including echocardiography and FDG-PET/CT aimed at detecting metastatic infectious foci can contribute to improved outcome.

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Abbreviations: CI = confidence interval, CRP = C-reactive protein, CT = computed tomography, FDG-PET/CT = ^{18}F-fluorodeoxyglucose-positron emission tomography in combination with low-dose computed tomography, MRI = magnetic resonance imaging, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

INTRODUCTION

An important complication of Gram-positive bacteremia is the presence of complicating metastatic infectious foci both by hematogenous and local spreading beyond the anatomic boundaries of the primary source of infection. Reported incidence of complicating foci varies between 16% and 36%.[8,9,15,17,20,26] Early detection of metastatic foci is important as morbidity and mortality are higher in the presence of these foci, probably due to incomplete eradication during initial treatment.[17] However, metastatic foci are often asymptomatic. In up to one-third of patients with Gram-positive bacteremia and metastatic foci, localizing signs and symptoms are absent.[7] In a Danish study, more than half of all patients admitted with *Staphylococcus aureus* spondylodiscitis had no symptoms suggesting this diagnosis at the time of admission.[16]

Treatment delay and community acquisition (which is probably a surrogate marker of delayed treatment) are the most important risk factors for the development of metastatic infection.[9,10,24] Persistently positive blood cultures and fever despite appropriate antibiotic treatment have a predictive value for the presence of such complicating foci.[9,22] It has been suggested that an intensive search for the presence of metastatic foci reduces relapse rates of infection and mortality.[18] However, conventional radiologic techniques would require the presence of guiding symptoms as only a fixed part of the body is visualized. Nuclear imaging techniques, such as whole body ^{18}F-fluorodeoxyglucose-positron emission tomography in combination with low-dose computed tomography scanning for optimizing anatomical correlation (FDG-PET/CT), might overcome this problem.[28,29] FDG-PET/CT is able to visualize localized foci of infectious and noninfectious inflammation, and has proven to contribute to the diagnosis in patients with fever of unknown origin or bloodstream infections.[3,4,30] In a retrospective study of 40 patients with bloodstream infection and a high risk of complications, FDG-PET was used to diagnose a clinically relevant new focus in 45% of cases, while, on average, 4 conventional diagnostic tests had already been performed previously. To our knowledge, at this time there are no guidelines describing a diagnostic protocol for the detection of metastatic infectious foci in patients with Gram-positive bacteremia, except for the recommendation to perform echocardiography in patients with *S. aureus* bacteremia.

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Figures 1 and 2 can be viewed in color online at http://www.md-journal.com.

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Here we present a prospective study in patients with *S. aureus* or *Streptococcus* species bacteremia with at least 1 risk factor for the development of metastatic foci. Based on previous studies, FDG-PET/CT was routinely added to the diagnostic workup including echocardiography. We evaluated the outcome and contribution of all diagnostic procedures, identified risk factors for developing metastatic infection, and assessed the relation between the presence of metastatic infection and clinical outcome.

PATIENTS AND METHODS

Patients

The current study was part of a prospective matched case-control study evaluating the utility of FDG-PET/CT for the detection of metastatic infectious foci in high-risk patients with Gram-positive bacteremia (International Standard Randomised Controlled Trial Number [ISRCTN] 76425553). From November 2005 until January 2008, patients were recruited from the Radboud University Nijmegen Medical Center, a 950-bed university hospital. Charts of all subsequent adult patients were reviewed within the first working day after a blood culture showed growth of *S. aureus* or *Streptococcus* species (excluding *S. pneumoniae*). Patients were eligible when a systemic inflammatory response syndrome was present at the time the blood culture was taken.[1] In addition, at least 1 of the known risk factors for the development of complicating infection had to be present, that is, community acquisition, signs of infection >48 hours before initiation of appropriate treatment (treatment delay), fever >72 hours after initiation of appropriate treatment, or positive blood cultures >48 hours after initiation of appropriate treatment. Patients with chemotherapy-induced neutropenia and pregnant women were excluded. The study was approved by the local ethics committee. Written informed consent was obtained from all patients.

Clinical Features

The portal of entry was defined as a localized site of infection preceding bacteremia. A central venous catheter was considered a portal of entry if there was evidence of inflammation at the insertion site or if culture of the catheter tip grew the same microorganism as the blood culture in the absence of evidence for another source of infection. Respiratory or urinary tract infections were diagnosed as portal of entry only when specific symptoms and signs were present in addition to positive culture results. Phlebitis due to peripheral intravascular catheters and cellulitis, categorized as skin infections, were considered as portals of entry, if present.

Bacteremia was defined to be nosocomial if only blood cultures taken after >48 hours of hospitalization were positive and clinical signs of the infection were absent at the time of admission. All other infections were considered community acquired. Both infectious foci without anatomic relation to the portal of entry and direct extension of the infection beyond the primary focus of infection were defined as complicating infectious foci. Endocarditis was defined according to the Duke criteria.[23] Prednisone ≥10 mg, or its equivalent dose of corticosteroids, was considered immunosuppressive treatment.

Metastatic infectious foci that were not diagnosed during the first period of infection, or a second period of bacteremia with the same microorganism, both within 3 months of the first positive blood culture, were defined as relapse of infection. Patients were considered cured if no symptoms or signs of infection were present 3 months after discontinuation of antibiotic treatment.

Diagnostic Workup

All patients were visited by an infectious diseases specialist for physical examination. Echocardiography was recommended. Transthoracic echocardiography (TTE) was used as a first-line screening technique, except for those patients with prosthetic valves, in whom transesophageal echocardiography (TEE) was the first-line technique. TEE was advocated in all patients in whom TTE was unremarkable, especially when imaging was hampered due to technical or anatomical problems. FGD-PET/CT was performed within 2 weeks after the first positive blood culture in all patients who gave written informed consent. Further diagnostic procedures like ultrasound, CT, and magnetic resonance imaging (MRI) were requested only in the presence of guiding signs or symptoms, or for confirmation of FDG-PET/CT findings. For treatment monitoring, C-reactive protein (CRP) and leukocyte counts were performed twice weekly. Blood culture samples were taken daily until 3 days after appropriate treatment had started and continued every other day as long as blood culture results remained positive.

Diagnosis and Patient Follow-Up

Patient follow-up ended 6 months after the first positive blood culture. Standard duration of antibiotic treatment in patients with uncomplicated bacteremia was 14 days. Treatment duration was extended to 6–12 weeks in case of infectious complications, depending on the localization and guidelines. Endocarditis was treated according to American Heart Association guidelines.[5] The final diagnosis was established by the attending physician and the first and last author (FJV and CPBR). The presence of metastatic infectious foci was based on the combination of clinical findings and results of conventional radiologic techniques. Wherever possible, samples were taken for culture and/or pathology and served as final proof. Because FDG-PET/CT is not an established imaging technique for some types of infectious foci that were diagnosed, a final diagnosis was never based on FDG-PET/CT findings alone.

Data Collection and Statistical Analysis

All epidemiologic data as well as diagnostic procedures and treatment data were collected in a structured database (Microsoft Access). Descriptive statistics for continuous variables are presented as means ± standard deviations. Differences between groups were tested with unpaired Student t-tests for continuous variables and with Fisher exact tests for categorical variables. Differences were considered to be statistically significant at $p < 0.05$. Sensitivity and specificity were calculated with 95% confidence intervals (CIs). A parameter was considered to be a significant predicting factor when the 95% CI of the relative risk was >1.

RESULTS

A total of 177 patients with either *S. aureus* or *Streptococcus* species bacteremia were identified during the study period. Of these patients, 53 had none of the predefined risk factors for the presence of metastatic infection. Nine patients refused informed consent, and 115 patients were included in the study (85 *S. aureus*, 13 hemolytic streptococci, 17 viridans streptococci). Most infections (72%) were community acquired (Table 1). Characteristics of patients with *S. aureus* or *Streptococcus* species differed in several aspects. Compared to the *Streptococcus* group, patients in the *S. aureus* group were more often primarily admitted to the intensive care unit (24% vs. 0%, $p = 0.02$), blood cultures remained positive for >48 hours after initiation of therapy more often (25% vs. 7%, $p = 0.03$), and significantly more patients

TABLE 1. Baseline Characteristics of High-Risk Patients With Gram-Positive Bacteremia

Characteristic	All Patients (n = 115) No. (%)	*Staphylococcus aureus* (n = 85) No. (%)	*Streptococcus* spp. (n = 30) No. (%)	P
Mean age, yr (± SD)	59 ± 15	59 ± 15	59 ± 15	
Male	67 (58)	52 (61)	15 (50)	0.29
Community acquisition	83 (72)	58 (68)	25 (83)	0.15
Primary ICU admission	20 (17)	20 (24)	0 (0)	0.02
Treatment delay >48 h*	83 (72)	59 (69)	24 (80)	0.35
Positive blood cultures >48 h after treatment	23 (20)	21 (25)	2 (7)	0.03
Fever >72 h	62 (54)	52 (61)	10 (33)	0.01
CVC present on admission	12 (10)	6 (7)	6 (20)	0.08
Diabetes mellitus	29 (25)	21 (25)	8 (27)	0.81
Malignancy	14 (12)	11 (13)	3 (10)	1.0
Immunosuppression	22 (19)	17 (20)	5 (17)	0.79
Dialysis	4 (3)	3 (4)	1 (3)	1.0
Alcohol abuse	6 (5)	4 (5)	2 (7)	0.65
Joint prosthesis	16 (14)	14 (16)	2 (7)	0.23
Cardiac valve prosthesis	9 (8)	7 (8)	2 (7)	1.0
Vascular prosthesis	14 (12)	11 (13)	3 (10)	1.0
Pacemaker	7 (6)	4 (5)	3 (10)	0.38

Abbreviations: ICU = intensive care unit, CVC = central venous catheter.

*Delay between first clinical signs of infection and initiation of treatment.

suffered from persistent fever >72 hours after the start of therapy (61% vs. 33%). The portal of entry was unknown in more than half of all patients (61/115, 53%), significantly more often in patients with *Streptococcus* species bacteremia than *S. aureus* bacteremia (70% vs. 47%, p = 0.04) (Table 2). Skin infections were most often diagnosed as the portal of entry, especially in patients with *S. aureus* bacteremia.

TABLE 2. Portal of Entry of Bacteremia

Portal of Entry	All Patients (n = 115) No. (%)	*Staphylococcus aureus* (n = 85) No. (%)	*Streptococcus* spp. (n = 30) No. (%)	P
Unknown	61 (53)	40 (47)	21 (70)	0.04
Known	54 (47)	45 (53)	9 (30)	
CVC	7	4	3	0.37
Skin infection	16	14	2	0.23
Pulmonary infection	5	5	0	0.32
Urinary tract infection	4	4	0	0.57
Wound infection	11	10	1	0.59
Other*	11	8	3	1.0

Abbreviations: CVC = central venous catheter.

*Other = manipulation urinary tract (2), colitis (2), endometritis (2), cholangitis, puncture carinal nodes, steroid injection bursa trochanterica, known fistula osteomyelitis, meningitis.

Metastatic infectious foci were detected in 84 of 115 (73%) patients (Table 3). The portal of entry was known in only 38% of patients, and an unknown portal of entry was a significant risk factor for developing metastatic foci (odds ratio, 5.6; 95% CI, 2.3–13.8). Mean CRP levels on admission were significantly higher in patients with metastatic infectious foci: 74 (95% CI, 45–103 mg/mL) vs. 160 mg/mL (95% CI, 132–188 mg/mL), p < 0.01. The maximal CRP levels during admission did not differ significantly between the 2 groups: 172 mg/mL (95% CI, 127–217 mg/mL) vs. 224 mg/mL (95% CI, 197–251 mg/mL), p = 0.53). Treatment delay of >48 hours was a strong predictor for developing metastatic infectious foci (p < 0.01). In total, 131 metastatic infectious foci were diagnosed in 84 patients (Table 4). The incidence of metastatic infection was similar in patients with *Streptococcus* species and patients with *S. aureus* bacteremia. Endocarditis, endovascular infections, pulmonary abscesses, and spondylodiscitis were diagnosed most frequently (see Table 4) (Figure 1). Pulmonary foci were found significantly more often in patients with *S. aureus* bacteremia than in those with *Streptococcus* species bacteremia (p = 0.01). In 30 (26%) patients, more than 1 complicating focus of infection was present. In 13 of 22 (59%) patients with endocarditis, another metastatic focus of infection was detected (Figure 2). All 22 endocarditis cases were proven according to the Duke criteria.[23] Symptoms guiding the attending physician in the diagnostic workup were present in only a minority of cases (41%). Fifty-six foci were diagnosed by either culture or pathology results. The remaining 53 foci were diagnosed using a combination of clinical examination and conventional radiologic techniques.

FDG-PET was performed in 102 patients, echocardiography in 85, CT in 60, ultrasound in 56, and MRI in 20 patients (Table 5). FDG-PET was the first to localize metastatic infectious foci in 35 of 115 (30%) patients, most of whom had no guiding symptoms. In 4 patients FDG-PET was false positive, resulting in a positive predictive value of 96%. In 1 patient with

TABLE 3. Possible Risk Factors for the Presence of Metastatic Infectious Foci

Risk Factor	Metastatic Focus Present (n = 84) No. (%)	Metastatic Focus Absent (n = 31) No. (%)	P	Odds Ratio (95% CI)
Community acquisition	63 (75)	20 (65)	0.35	1.6 (0.6–4.0)
Treatment delay >48 h	68 (81)	14 (45)	<0.01	5.6 (2.3–13.8)
Blood cultures >48 h	20 (24)	3 (10)	0.12	2.9 (0.8–10.6)
Fever >72 h	50 (60)	12 (39)	0.06	2.3 (1.0–5.4)
CVC present on admission	6 (7)	6 (19)	0.08	0.3 (0.1–1.1)
Portal of entry unknown	52 (62)	9 (29)	0.03	4.0 (1.6–9.7)
Diabetes mellitus	22 (26)	7 (23)	0.81	1.22 (0.5–3.2)
Malignancy	8 (10)	6 (19)	0.2	0.4 (0.1–1.4)
Immunosuppression	16 (19)	6 (19)	1.0	1.0 (0.4–2.8)
Alcoholism	3 (4)	3 (10)	0.34	0.4 (0.1–1.8)
Foreign body material	31 (37)	5 (16)	0.04	3.0 (1.1–8.7)
S. aureus	64 (76)	21 (68)	0.47	1.5 (0.6–3.7)
Age >60 yr	47 (56)	18 (58)	0.83	1.1 (0.5–2.6)

Abbreviations: CVC = central venous catheter.

endocarditis, abnormal uptake in the right shoulder was due to tendinitis. Abnormal FDG-uptake was caused by a sterile hemorrhage in the psoas muscle during anticoagulant use in a second patient. False-positive uptake in the colonic wall was seen in 1 patient, and 1 patient died before further investigations could be performed to confirm abnormal pleural FDG-uptake. She had possible endocarditis and pleural effusion with persistently positive blood cultures. The negative predictive value was 98% when only those foci situated inside the area scanned by FDG-PET were counted (see Table 5). In 1 patient, a pacemaker lead infection was missed by FDG-PET. Another 10 foci were not revealed; however, these foci were situated in the central nervous system in 5 patients, and in the distal extremities in the other 5 patients. These areas are not captured by routine PET scanning. In all 10 patients in whom FDG-PET did not reveal metastatic infectious foci, guiding signs and symptoms directed the attending physician to perform further investigations.

Routine echocardiography, performed in 86 patients, supported the presence of endocarditis in 22 (26%) cases. TTE was performed in 77 patients, with 43 followed by TEE. A primary

TABLE 4. Localization of Metastatic Infectious Foci and Presence of Guiding Signs and Symptoms

Localization	All Patients (n = 115) No. (%)	Guiding Signs and Symptoms No.	*Staphylococcus aureus* (n = 85) No. (%)	*Streptococcus* spp. (n = 30) No. (%)	P
Not present, no. of patients	31 (27)		21 (25)	10 (33)	
Present, no. of patients	84 (73)		64 (75)	20 (67)	0.47
Endocarditis	22	0	13	9	0.1
Endovascular*	19	5	11	8	0.09
Lung	16	5	16	0	0.01
Liver	2	1	1	1	0.46
Spleen	3	0	3	0	0.57
Joint	9	8	8	1	0.44
Osteomyelitis	6	4	5	1	1.0
Spondylodiscitis	11	8	10	1	0.28
Psoas	4	1	3	1	1.0
Soft tissue	11	6	11	0	0.06
Central nervous system	11	11	8	3	1.0
Eye	3	3	1	2	0.17
Prosthetic joint	10	8	8	2	1.0
Intraabdominal	3	1	2	1	1.0
Kidney	1	1	1	0	1.0
Total number of metastatic foci	131	54	101	30	

*Bentall prosthesis aortic arch (2), aortic prosthesis (3), mycotic aneurism aorta (3), mycotic aneurism femoral artery (2), subclavian vein after line removal (4), pacemaker lead (1), mycotic aneurism iliac artery (1), septic thrombophlebitis femoral vein (2), pylephlebitis (1).

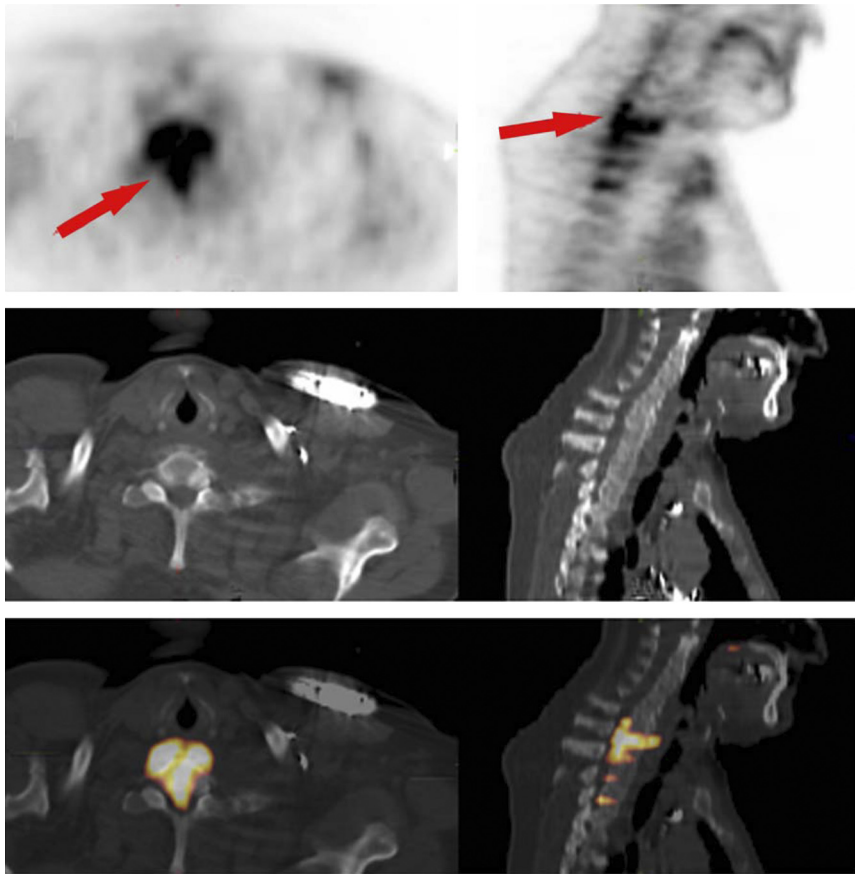

FIGURE 1. A 65-year-old man with *Staphylococcus aureus* bacteremia and persistent fever despite antibiotic therapy. Top to bottom, FDG-PET, CT, and fusion; left, transverse; right, sagittal slices. FDG-PET/CT shows abnormal FDG uptake (arrows) compatible with C6-7 spondylodiscitis and spreading inside the spinal canal compatible with an epidural abscess. The latter was confirmed on CT myelography. MRI was not possible due to the patient's intracardial defibrillator. [This figure can be viewed in color online at http://www.md-journal.com.]

TEE was performed in 9 patients. Sign and symptom-guided CT, ultrasound, and MRI reached excellent specificity and positive predictive values with high sensitivity and negative predictive values (see Table 5). As only a minority of foci were accompanied by guiding signs and symptoms, the number of foci revealed by CT, ultrasound, and MRI remained low.

Risk factors for mortality are listed in Table 6. Persistently positive blood cultures >48 hours after starting treatment, nosocomial infection, and age above 60 years were associated with increased mortality. Treatment delay was not associated with mortality. Median duration of treatment differed significantly between patients with or without metastatic infectious foci (44 vs. 15 d, respectively) (Table 7). Mortality tended to be lower in patients without complicated infection (25% vs. 16%), albeit not significantly.

Five of 31 patients without proven metastatic foci died (16%). In retrospect, of these 5 patients, 3 likely had metastatic foci that could not be diagnosed during life. The first patient had a possible endocarditis (persistently positive blood cultures, continuing fever, Janeway lesions, and changed systolic murmur). He died before echocardiography was performed. The second patient had persistently positive blood cultures during 72 hours despite high-dose flucloxacillin and persistent pyuria growing *S. aureus*. This patient refused any further investigations. Antibiotic treatment was stopped on his request after 15 days. He died 2 weeks after discharge in a nursing home having documented high fevers during the weeks before his death. The third patient had positive blood cultures with *S. aureus* and splinter hemorrhages 3 days after a pacemaker implantation. Only TTE was performed, which did not reveal any signs of endocarditis or pacemaker lead infection. TEE was refused by the patient, and the pacemaker was not removed. This patient died while on antibiotic treatment 36 days after admission due to cardiac failure. Autopsy was refused. If these 3 patients are presumed to have had metastatic foci, then only 2 patients died in the absence of metastatic infectious foci. One of these patients died on day 2 because of septic shock, and the other patient died on day 24 after admission with end-stage laryngeal carcinoma.

DISCUSSION

In the current prospective cohort study, the vast majority of high-risk patients with Gram-positive bacteremia developed metastatic infectious foci (73%), of which more than 40% were clinically silent. Mortality rates might be decreased by an active search for and treatment of clinically silent foci, as mortality tended to be higher in the presence of metastatic infectious foci.

Earlier studies, which did not specifically address high-risk patients, have reported an incidence of metastatic foci ranging from 16% to 36% (Table 8).[7,17,20,21,26,27] Patients in the current study were selected based on the presence of 4 well-known clinical risk factors for the development of complicated

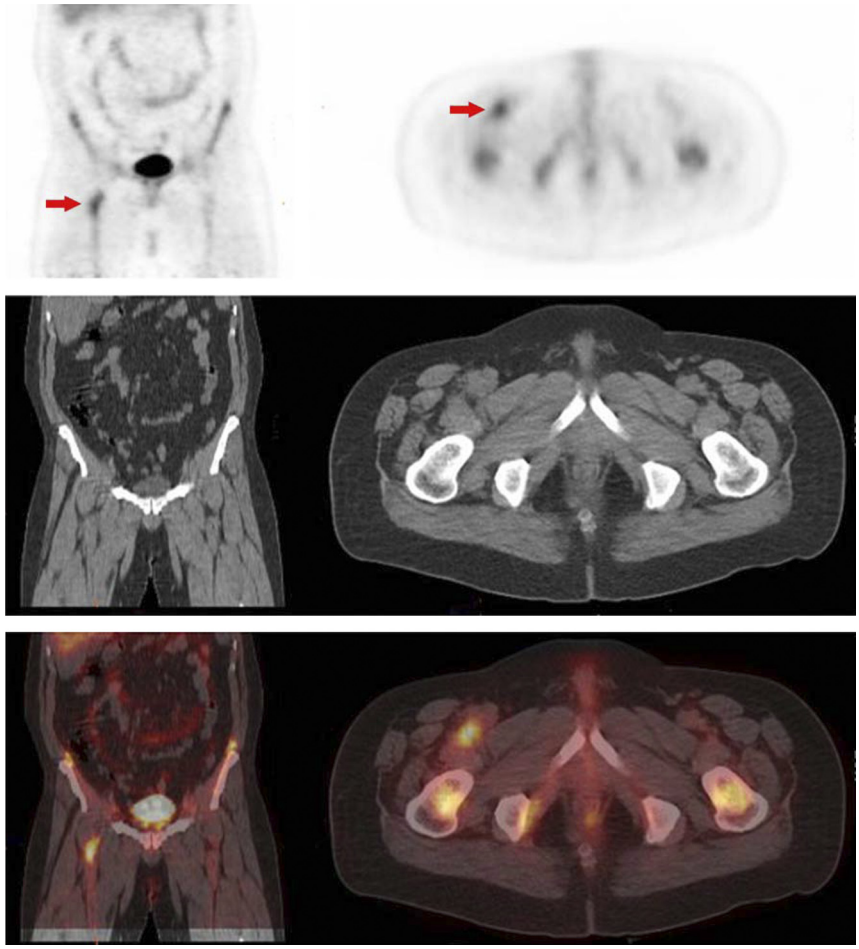

FIGURE 2. Mycotic aneurysm of the a. femoralis profunda in a 49-year-old man with *Staphylococcus aureus* bacteremia and endocarditis. Top to bottom, FDG-PET, CT, and fusion; left, coronal; right, transverse slices. FDG-PET/CT shows abnormal FDG uptake (arrows) compatible with vascular infection. [This figure can be viewed in color online at http://www.md-journal.com.]

infection.[9,10,21,24] These differences in patient characteristics may hamper a direct comparison between studies, but the active search in the current study aimed at early identification of metastatic foci most likely contributed to the much higher yield of metastatic infections. The active approach using FDG-PET/CT and echocardiography in the first 2 weeks of admission in high-risk patients with Gram-positive bacteremia revealed significantly more metastatic foci compared to a matched control group in whom the diagnostic regimen was symptom guided and led to significantly lower mortality rates.[30] Three earlier studies have reported that significantly fewer metastatic foci could be diagnosed in patients in whom recommendations of an infectious disease specialist were not followed.[8,15,26] Most importantly, this was due to the failure to perform supplementary investigations such as echocardiography and surveillance blood cultures.

Positive blood cultures during follow-up after the start of antimicrobial therapy have been found to be a predictor of metastatic infectious disease.[22] In the present study we identified delayed initiation of treatment, the presence of foreign body material, and an unknown portal of entry for infection as risk factors for the development of metastatic foci. Of patients with an unknown portal of entry, 52 of 61 (82%) developed proven

TABLE 5. Diagnostic Utility of Imaging Techniques Contributing to Diagnosis of Metastatic Infectious Foci

Technique	No. of Examinations	Contributory No. (%)	Sensitivity %	Specificity %	PPV %	NPV %
FDG-PET	102	61 (60)	99	92	96	98
CT scan*	60	32 (53)	94	100	100	93
Ultrasound*	56	19 (34)	95	100	100	96
MRI*	20	12 (60)	92	100	100	88

*CT, ultrasound, and MRI were performed only in case of guiding signs or symptoms and when suitable for the area to be investigated: chest CT in 21, abdominal CT in 24, central nervous system (CNS) CT in 11, soft tissue CT in 4, abdominal ultrasound in 30, soft tissue ultrasound in 25, CNS MRI in 13, and soft tissue MRI in 8 patients. FDG-PET was the only diagnostic technique routinely performed for screening purposes.

TABLE 6. Risk Factors for Mortality at 6 Month Follow-Up

Risk Factor	Survivors (n = 89) No. (%)	Died (n = 26) No. (%)	P
Community acquisition	69 (78)	14 (54)	0.03
Treatment delay >48 h	63 (71)	20 (77)	0.63
Positive blood cultures >48 h	14 (16)	9 (35)	0.05
Fever >72 h	47 (53)	15 (58)	0.82
CVC present on admission	9 (10)	3 (12)	1.0
Portal of entry unknown	44 (49)	10 (38)	0.38
Diabetes mellitus	19 (21)	10 (38)	0.12
Malignancy	11 (12)	3 (12)	1.0
Immunosuppression	13 (14)	9 (35)	0.43
Alcoholism	5 (6)	1 (4)	1.0
Foreign body material	26 (29)	10 (38)	0.47
S. aureus	63 (71)	23 (88)	0.08
Age >60 yr	44 (49)	21 (81)	<0.01

Abbreviations: CVC = central venous catheter.

metastatic infection, versus 32 of 54 (59%) patients admitted with a known portal of entry. CRP levels on admission tended to be higher in patients with metastatic foci; however, the maximal CRP level during admission did not differ between patient groups. Most likely, the CRP level on admission reflects the duration of illness on admission and therefore is a surrogate marker for treatment delay. As some overlap in CRP levels on admission was found between groups with and without metastatic infectious foci, CRP levels should be interpreted only in relation to the patient's history, for example regarding treatment delay, which probably leads to a higher CRP upon admission.

It is important to realize that only 41% of metastatic foci were associated with clear signs or symptoms guiding the physician to a diagnosis. Especially deep soft tissue infections, endovascular, and pulmonary foci lacked guiding symptoms. When ordered based on symptoms, CT, MRI, and ultrasound have high predictive values. However, as only a minority of patients had guiding signs or symptoms, only a minority of foci (9%–24%) could be identified using CT, MRI, and ultrasound. In contrast, routinely performed FDG-PET revealed 69% of all metastatic infectious foci that were identified. In approximately 30% of patients, FDG-PET/CT revealed at least 1 clinically silent infectious metastatic focus. This is in accord with studies on fever of unknown origin, in which whole body FDG-PET proved to be superior when compared to routinely performed combined chest and abdominal CT.[3,6] In a retrospective study on the detection of metastatic foci, FDG-PET revealed a significant number of new relevant foci even after a total of 4 conventional imaging techniques had been performed.[2] The superiority of FDG-PET/CT is not only due to whole body imaging, but also because FDG-PET provides functional information in contrast to CT, and, to a lesser extent, to MRI. Previously, FDG-PET also proved to be superior in postoperative wound infections and vascular graft infections when compared to CT scanning, and in spondylodiscitis when compared to MRI.[11,13,19,25,31] The most important technical drawback in FDG-PET compared to CT and MRI is the lower spatial resolution (3-5 mm compared to 1–2 mm). In suspected epidural extension accompanying spondylodiscitis, MRI might be contributory. CT, ultrasound, and MRI therefore are not suitable as a screening technique to detect metastatic infectious foci in patients with a high probability of having these infectious complications, because only a limited part of the body is scanned.[12] Routine echocardiography revealed vegetations in approximately one-quarter of patients who underwent echocardiography.

Mortality rates in patients with Gram-positive bacteremia are high. We speculated that a more rigorous search for metastatic infection could influence outcome by decreasing relapse rates and mortality rates, and this has indeed been confirmed in our prospective matched case-control study,[30] in which the diagnostic work-up was symptom guided and only routine echocardiography was advocated, according to guidelines.[5] Compared with rates of the control group in that study, relapse rates in patients with *S. aureus* bacteremia were significantly lower in the study group (8.9% vs. 1.4%, $p = 0.04$), as was mortality (30% vs. 19%, $p < 0.01$). This underscores that appropriate and early diagnosis of metastatic infectious foci is important for adequate treatment of these patients, for example by timely initiation of antibiotic treatment, prolongation of antibiotic treatment, or drainage of abscesses. The extra costs related to treating the increased number of metastatic infectious foci in high-risk patients are balanced by the reduction of re-admissions due to relapse of infection or protracted cure.[30a] To our knowledge, at this time there are no guidelines describing a diagnostic protocol for the detection of metastatic infectious foci in patients with Gram-positive bacteremia, except for the recommendation to perform echocardiography in patients with *S. aureus* bacteremia. It has been shown before that metastatic infectious foci can be detected in most parts of the body by FDG-PET scanning, and therefore FDG-PET was included on a routine basis in the diagnostic protocol of our study.[3,30]

Earlier studies in patients with Gram-positive bacteremia have also reported high mortality rates, especially in patients with *S. aureus* bacteremia, varying between 9% and 38%.[8,9,17,20,26,27] Only sparse information on mortality rates among patients with streptococcal bacteremia is available. In patients with bacteremia due to hemolytic group A and G streptococci, mortality rates varied between 14% and 23%.[2,14] In a

TABLE 7. Patient Outcomes at 6 Month Follow-Up

Outcome	Total Metastatic Foci		*Staphylococcus aureus* Metastatic Foci		*Streptococcus* spp. Metastatic Foci	
	Present (n = 84) No. (%)	Absent (n = 31) No. (%)	Present (n = 64) No. (%)	Absent (n = 21) No. (%)	Present (n = 20) No. (%)	Absent (n = 10) No. (%)
Median treatment duration (d)	44	15	42	15	48	13
Mortality	21 (25)	5 (16)	19 (30)	4 (19)	2 (10)	1 (10)

TABLE 8. Series of Gram-Positive Bacteremia, Present and Previous Reports

First Author (Country)	Design	Microorganism	No. of Patients (Recruitment Period)	Metastatic Foci %
Lautenschlager (Switzerland)[20]	Retrospective, hospital based, 1 UH, ID consultancy	SAB	281 (1980–1986)	27
Lesens (France)[21]	Retrospective, internal medicine department, 1 UH	SAB	109 (1992–1999)	25
Jensen (Denmark)[17]	Prospective, hospital based, 4 CH, ID consultancy	SAB	186 (1994–1996)	16
Fowler (US)[8]	Prospective, hospital based, 1 UH, ID consultancy	SAB	244 (1994–1996)	30
Verhagen (Netherlands)[27]	Retrospective, hospital based, 1 UH	SAB	79 (1999–2000)	38
Cuijpers (Netherlands)[7]	Retrospective, hospital based, 1 UH	SAB+SSB	180 (2002–2004)	34
Rieg (Germany)[26]	Retrospective/prospective, hospital based, 1 UH, ID consultancy	SAB	521 (2002–2007)	36
Vos (Netherlands)[PR, 30]	Prospective, hospital based, high-risk patients selected, 1 UH, ID consultancy, routine FDG-PET/CT and echocardiography	SAB+SSB	115 (2005–2008)	73

Abbreviations: CH = community hospital, ID consultancy = infectious diseases specialist consultancy, PR = present report, UH = university hospital, SAB = *S. aureus* bacteremia, SSB = *Streptococcus* spp. bacteremia.

recent series of 53 patients with *Streptococcus* species bacteremia, mortality was 11%.[7]

In the present study among patients with Gram-positive bacteremia, persistently positive blood cultures and older age were associated with increased mortality rates, as were nosocomial infections. In contrast to other studies, treatment delay and community acquisition were not associated with increased mortality. Two possible explanations come to mind. First, patients were selected using a set of 4 known clinical parameters predicting complicated infection, among which treatment delay and community acquisition both were present in approximately 75% of patients. The study therefore was not designed to identify risk factors for complicated outcome. Treatment delay, on the other hand, was a strong predictor for the presence of metastatic infectious foci, which were treated accordingly, and death might have been prevented. Since an intensive search for the presence of metastatic foci was performed, it is possible that no relation between treatment delay and mortality was found. Lautenschlager already reported that complicated infection was associated with increased mortality rates, which has been confirmed in other studies.[8,17,20] In these studies, complicated infection was defined as a combination of metastatic foci of infection, relapse, or the inability to remove the primary focus of infection. An important explanation for treatment failure in these studies was the delayed start of appropriate treatment in patients without an identifiable focus of infection. In a retrospective survey of 281 patients with *S. aureus* bacteremia, bacteremia was judged insignificant in 19% until a metastatic focus of infection was detected.[20] Treatment delay for more than 45 hours was associated with increased mortality in a retrospective cohort of 167 patients with hospital-acquired *S. aureus* bacteremia.[24] Finally, inappropriate focus eradication has been associated with relapse of infection and mortality in other studies.[7,17] These studies suggest that identifying metastatic foci of infection may be an important tool to improve treatment outcome in patients with Gram-positive bacteremia.

In conclusion, the present study has demonstrated 2 important issues: first, after an intensive search aimed at detecting metastatic infectious foci, the majority of high-risk patients with Gram-positive bacteremia did have metastatic foci. Second, the majority of these metastatic foci did not have guiding signs or symptoms, which can lead to incomplete focus eradication. Thus in patients with Gram-positive bacteremia and a high risk for developing complicated infection (community acquisition, treatment delay, persistently positive blood cultures >48 h, and persistent fever >72 h after initiation of treatment), a structured protocol including echocardiography and FDG-PET aimed at detecting metastatic infectious foci may contribute to improved outcome.

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